pathogenesis of pre-eruptive neurological complications of varicella continues to be essentially unknown.

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Histiocytic Medullary Reticulosis in Two Chinese Women

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HISTIOCYTIC MEDULLARY RETICULOSIS (HMR) is a rare hematological malignant disease. Only 60 cases have been reported. Scott and Robb-Smith were the first to recognize HMR as a distinct entity when they reported six cases in 1939.[1] Since then various observers have reported sporadic cases and these combined reports have given rise to a concept of the clinical and morphological features of HMR. There are no pathognomonic findings; diagnosis comes from suggestive clinical features coupled with morphologic characteristics.

Clinically, HMR may be insidious in onset, with fatigue and weight loss the only early symptoms, but often the patients present with hectic fevers and night sweats. Fever at some time in the early course of the disease is a characteristic feature and tends to be moderate to severe and either intermittent or unrelenting. Common physical findings in HMR are moderate to pronounced and progressive splenomegaly, reported in more than 90 percent of patients, hepatomegaly in 75 percent, and a surprising absence of widespread lymphadenopathy in most cases.[2-4]

The hematological findings of HMR follow a characteristic pattern with the vast majority of patients presenting with pancytopenia of the peripheral blood. The anemia, normochromic and normocytic, is commonly associated with a hemoglobin of less than 10 grams per 100 ml. The thrombocytopenia is usually moderate and although bleeding is not typical in HMR, it can occur. The neutropenia is in the range of 2,000 to 2,500 cells per cu mm and the differential is usually normal. Bone marrow examination typically reveals a diffuse increase of histiocytes, these cells often making up from 10 to 80 percent of the marrow elements. As many as 10 to 20 percent of the histiocytes will be engaged in phagocytosis, primarily of erythroid elements, but phagocytosis of platelets and myeloid elements is also common. The demonstration of phagocytosis represents the characteristic morphologic feature of HMR and this must be observed before a diagnosis is made. Additional marrow findings usually include erythroid hyperplasia and abundant megakaryocytes.

Biopsy of the liver and autopsy specimens of liver, spleen, and often other reticuloendothelial tissue likewise reveals an increase in histiocytes engaged in phagocytosis of erythroid, myeloid, and platelet elements. Phagocytosis of these elements by histiocytes is thought, by most observers, to account for the anemia, neutropenia, and thrombocytopenia of HMR.[5,6] Although several reports have mentioned the finding of occasional histiocytic cells in the peripheral blood, a leukemic phase of this disease has not been reported.

Clinically, HMR is a rapidly fatal disease which remains unresponsive to therapy and death usually occurs within a year of the diagnosis. Numerous cytotoxic agents have been tried in this disorder, but remissions, if induced at all, have been very brief and no chemotherapeutic regimen has been uniformly successful in improving survival. Radiation therapy is not commented upon in many reports, and when it was employed the benefit was not clear.

The largest single series of HMR comes from China and assembles the entire Chinese experience

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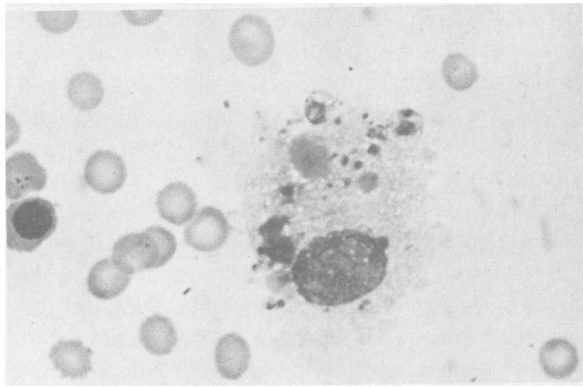

Figure 1.—Marrow histiocyte (Case 1) showing phagocytosis of erythrocytes, platelets, and probably two neutrophils.

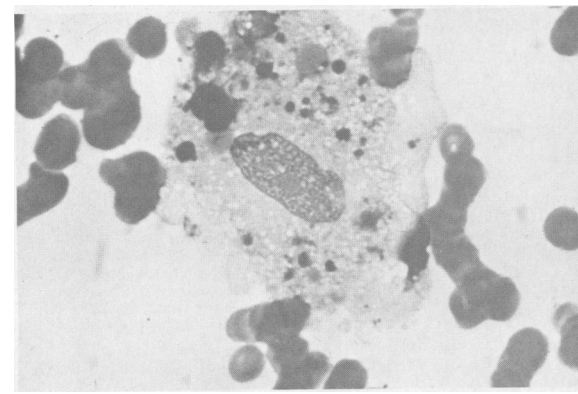

Figure 2.—Marrow histiocyte (Case 1) showing phagocytosis of erythrocyte, myelocyte, and numerous platelets.

with this disorder; in this series of 18 cases there was only one female patient.[4]

The two cases here reported were in Chinese-born women with the characteristic clinical and morphological features of HMR.

Reports of Cases

CASE 1. A 50-year-old Chinese woman consulted a private physician, two years before final admission, with complaint of a mass in the right side of the neck. Biopsy showed a node was supplanted by abnormal cells which were thought to represent lymphoblastic lymphoma. At that time a blood cell count was within normal limits with leukocytes 5,200 per cu mm, hemoglobin 12 grams per 100 ml, the hematocrit 37 percent, and the platelet count 125,000 per cu mm. A bone marrow examination was interpreted as normal. The patient was treated with irradiation, 2,500 R to the right side of the neck. She remained well for 24 months and then suddenly became ill with chills, night sweats, and fever of 40°C (104°F). At that time she was found to have significant hepatosplenomegaly and abdominal distension. Hemoglobin content was 8 grams per 100 ml of blood, the hematocrit 23 percent, leukocyte count of 4,400 per cu mm, and platelets 120,000 per cu mm. A bone marrow specimen was interpreted as normal by a pathologist. Suspecting relapse of lymphoma, the attending physician prescribed COP [cyclophosphamide + vincristine sulfate (Oncovin®) + prednisone] cyclic chemotherapy every three weeks as described by Luce and associates.[7] The course of illness remained unchanged for the following month except for progressive pancytopenia (hemoglobin 6 grams per 100 ml, leukocytes 4,000 per cu mm, and platelets 65,000 per cu mm). Over the next six weeks the patient received two more courses of chemotherapy without resolution of fever, anemia or thrombocytopenia; and at that time she was found to have progressing hepatosplenomegaly but no lymphadenopathy. Platelets decreased to 21,000 per cu mm and transfusions were necessary to keep the hemoglobin content above 10 grams per 100 ml. She was then transferred to UCLA where the same findings were noted. She remained acutely ill, with fever to 40°C.

Numerous cultures were obtained including studies for cytomegalovirus, histoplasmosis, toxoplasmosis, and pneumocystis carinii. All such studies were negative and the fever remained unexplained. Administration of bleomycin sulphate (NSC 125066) was begun at a dose of 15 mg per square meter twice a week. At this time leukocytes numbered 1,500 per cu mm, hemoglobin was 9.6 grams per 100 ml, the hematocrit was 28 percent, and the platelet count 10,000 per cu mm. Liver function tests were abnormal, with pronounced elevation of the serum glutamic oxalic transaminase, lactic dehydrogenase and alkaline phosphatase. A bone marrow examination revealed a large number of histiocytes, accounting for approximately 20 percent of nucleated cells. Many of these histiocytes were engaged in phagocytosis of erythroid, myeloid, and thrombocyte elements. Representative examples of this phagocytosis are shown in Figures 1 and 2.

After three weeks of therapy (six doses of bleomycin) the patient had not improved and hepatosplenomegaly progressed without the development of lymphadenopathy. By the end of the third week of therapy the leukocyte count had decreased to 525 and the platelet count to 5,000

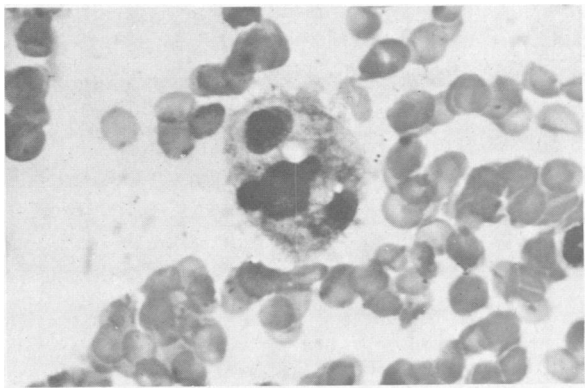

Figure 3.—Marrow histiocyte (Case 2) showing phagocytosis of two nucleated red cells and a segmented neutrophil.

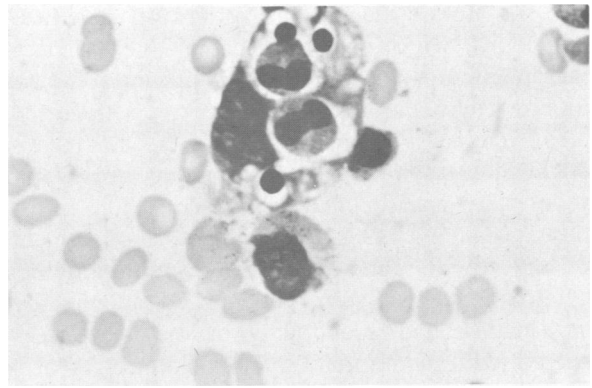

Figure 4.—Marrow histiocyte (Case 2) showing phagocytosis of two neutrophils and three nucleated erythrocytes.

per cu mm; and in spite of transfusions the hemoglobin was 8.9 grams per 100 ml. She died of respiratory failure at this time.

CASE 2. The patient, a 24-year-old Chinese woman, had been admitted to UCLA seven months before the final admission. On the initial she had had fever, chills, and profuse night sweats for three weeks and had had a lump in neck for one week. Her past history was negative except for a positive tuberculin skin test one year earlier, because of which she was receiving isoniazid. On physical examination at that time left cervical and right inguinal adenopathy were noted. Leukocytes numbered 2,700 and platelets 130,000 per cu mm, and the hemoglobin content was 10 grams per 100 ml. Results of liver function tests were abnormal, with elevation of the SGOT, SGPT, and alkaline phosphatase. Bilirubin, serum proteins and serum protein electrophoretic pattern were within normal limits. A liver-spleen scan showed moderate hepatomegaly but not splenomegaly. An x-ray film of the chest was normal and an intravenous pyelogram showed slight deviation of the right ureter. Numerous cultures were obtained and an investigation for infection included studies for cytomegalovirus, histoplasmosis, toxoplasmosis, and cultures for tuberculosis and fungi. None of these studies were positive and the fever remained unexplained.

Biopsy of the liver and of a left cervical lymph node showed diffuse histiocytosis, with erythrophagocytosis being noted in the liver specimens. Bone marrow examination was initially interpreted as showing only reactive myeloid elements. Because of the pathologic changes in the lymph node, and particularly the liver, the patient was diagnosed as having histiocytic lymphoma, suggestive of HMR, and was treated with cyclophosphamide 100 mg a day and prednisone 40 mg a day by mouth. She showed some symptomatic improvement but the lymphadenopathy progressed. Two months later the prednisone and cyclophosphamide were discontinued and irradiation was administered—4,500 R to the left cervical and right inguinal areas. During the following month adenopathy continued to progress and COP therapy as described in Case 1 was begun. There was then temporary resolution of adenopathy, but four weeks later it reappeared despite continued combination chemotherapy. At this time an abdominal mass developed and it progressed to obstruction of the small bowel. The patient then received 800 R to the abdomen with improvement in symptoms, and she was given BCNU (NSC-409962, bischlorethyl-nitrosourea) 150 mg on day one followed by 75 mg on day three. She had no objective response and died of pancytopenia and bleeding seven months after initial presentation. At autopsy, histiocytic involvement of cervical, axillary, mesenteric, and aortic lymph nodes was noted, as well as histiocytosis in the jejunum, epicardium, liver, right renal pelvis, right adrenal gland, left ovary and inferior vena cava. On careful reappraisal of the initial bone marrow material, diffuse histiocytosis was noted, with histiocytes accounting for approximately 15 percent of nucleated elements. Many of these histiocytes were engaged in phagocytosis of erythroid, myeloid, and platelet forms. Figures 3 and 4 demonstrate representative marrow findings.

Discussion

These two cases demonstrate the rather typical clinical course and characteristic marrow findings

of HMR. Both patients had a progressively downhill course which was little changed by chemotherapeutics. Neither showed significant response to COP combination chemotherapy; one received bleomycin and the other received BCNU, both without demonstrable benefit. Unrelenting febrile episodes were unassociated with a detectable infectious agent and neither patient had improvement of the febrile course with either antibiotic or cytotoxic therapy. One patient had adenopathy but neither had adenopathy of the degree expected with widespread lymphomatous disease. Both patients had pancytopenia which progressed to a striking degree regardless of therapy.

In both of these patients the bone marrow was initially thought to be normal by experienced pathologists; however, careful retrospective examination of initial marrow specimens from both patients revealed the characteristic changes of HMR. It is noteworthy that in the specimens of marrow from both patients the increase in histiocytes was usually noted in areas surrounding marrow particles and in peripheral areas of the marrow smear. Very few histiocytic cells were actually found in the cellular centers and, in general, the histiocytosis and phagocytosis, although quite striking, were obviously patchy. For this reason it is suggested that in all cases of suspected histiocytic lymphomas the marrow be examined painstakingly to detect phagocytosis of cellular elements which might not be apparent during routine examination of the most cellular marrow particles.

The cause of HMR is unknown but most investigators consider it a malignant disease; some suggest that it is an atypical variant of histiocytic lymphoma. The prognosis is poorer and the survival shorter than for histiocytic lymphoma, however, and a further point of difference is that phagocytosis of platelets, erythroid and myeloid elements is not a characteristic finding in histiocytic lymphoma.[8]

HMR bears an unclear relationship to leukemic reticuloendotheliosis (histiocytic leukemia) but the two might be related in the same manner as are well differentiated lymphocytic lymphoma and chronic lymphocytic leukemia. If HMR and leukemic reticuloendotheliosis are related, however, it is clear that the leukemic form has a much better prognosis than the medullary disorder. The marrow of leukemic reticuloendotheliosis is easily differentiated from that of HMR in that not only is phagocytosis not seen,[9] several investigators have clearly demonstrated the cells of leukemic reticuloendotheliosis to be incapable of phagocytosis.[10,11] Furthermore, the marrow of reticuloendotheliosis tends to be hypocellular, difficult to aspirate, and often fibrotic, whereas in HMR the marrow is usually hypercellular. Clear clinical differences also exist, with more than 60 percent of patients with leukemic reticuloendotheliosis pursuing a subacute or chronic course and survivals of ten years not uncommon.[12] Although both diseases are associated with hepatosplenomegaly, leukemic reticuloendotheliosis is characterized by widespread lymphadenopathy while HMR is not.

HMR is thought to represent a rare subgroup of histiocytic lymphoma but it may actually be found to be more common than has been suspected when bone marrow specimens are more carefully searched for the typical morphological features of this disorder. It seems important to identify this disease correctly since there are obvious prognostic and possibly different therapeutic implications. Our patients as well as those described in the literature were resistant to the usual chemotherapeutic agents used in the treatment of lymphomas. Both of our patients had beneficial effects from radiation therapy. Procarbazine (Matulane®), which we did not use, has been reported to have antihistiocytic activity.[13]

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